JACC Vol. 20, No. 2
August 1992:276–86

Alterations of Phasic Coronary Artery Flow Velocity in Humans During Percutaneous Coronary Angioplasty

JEROME SEGAL, MD, FACC, MORTON J. KERN, MD, FACC,*
NEAL A. SCOTT, MD, PHD, FACC,† SPENCER B. KING III, MD, FACC,†
JOSEPH W. DOUCETTE, MD,‡ RICHARD R. HEUSER, MD, FACC,§
ELIZABETH OFILI, MD,* ROBERT SIEGEL, MD§

Washington, D.C.; Saint Louis, Missouri; Atlanta, Georgia; Redwood City, California; Phoenix, Arizona

Background and Objectives. **Studies using Doppler catheters to assess blood flow velocity and vasodilator reserve in proximal coronary arteries have failed to demonstrate significant improvement immediately after coronary angioplasty. Measurement of blood flow velocity, flow reserve and phasic diastolic/systolic velocity ratio performed distal to a coronary stenosis may provide important information concerning the physiologic significance of coronary artery stenosis. This study was designed to measure these blood flow velocity variables both proximal and distal to a significant coronary artery stenosis in patients undergoing coronary angioplasty.**

Methods. **A low profile (0.018-in.) (0.046-cm) Doppler angioplasty guide wire capable of providing spectral flow velocity data was used to measure blood flow velocity, flow reserve and diastolic/systolic velocity ratio both proximal and distal to left anterior descending or left circumflex coronary artery stenosis. These measurements were made in 38 patients undergoing coronary angioplasty and in 12 patients without significant coronary artery disease.**

Results. **Significant improvement in mean time average peak velocity was noted in distal coronary arteries after angioplasty (before 19 ± 12 cm/s; after 35 ± 16 cm/s; $p < 0.01$). Increases in proximal average peak velocity after angioplasty were less remarkable (before 34 ± 18 cm/s; after 41 ± 14 cm/s; $p = 0.04$). Mean flow reserve remained unchanged after angioplasty both proximal (1.5 ± 0.5 vs. 1.6 ± 1; $p > 0.10$) and distal (1.6 ± 1 vs. 1.5 ± 0.8; $p > 0.10$) to a coronary stenosis. Before angioplasty, mean diastolic/systolic velocity ratio measured distal to a significant stenosis was decreased compared with that in normal vessels (1.3 ± 0.5 vs. 1.8 ± 0.5; $p < 0.01$). After angioplasty, distal abnormal phasic velocity patterns generally returned to normal, with a significant increase in mean diastolic/systolic velocity ratio (1.3 ± 0.5 vs. 1.9 ± 0.6; $p < 0.01$). Phasic velocity patterns and mean diastolic/systolic velocity ratio measured proximal to a coronary stenosis were not statistically different from values in normal vessels (1.8 ± 0.8 vs. 1.8 ± 0.5; $p > 0.10$) and did not change significantly after angioplasty (1.8 ± 0.8 vs. 2.13 ± 0.9; $p > 0.10$).**

Conclusions. **Flow velocity measurements may be performed distal to a coronary stenosis with the Doppler guide wire. Phasic velocity measurements made proximal to a coronary stenosis differed from those in the distal coronary artery. Both proximal and distal flow reserve measurements made immediately after angioplasty were of limited utility. Changes in distal flow velocity patterns and diastolic/systolic velocity ratio appeared to be more relevant than the hyperemic response in assessing the immediate physiologic outcome of coronary angioplasty.**

(J Am Coll Cardiol 1992;20:276–86)

Coronary artery pulsed Doppler catheters and intraoperatively placed coronary artery probes have been used to measure the velocity of blood flow in epicardial coronary arteries and to assess coronary vasodilator reserve in humans. Some studies (1,2) have demonstrated poor correlation of flow reserve with angiographic indexes of the severity of the stenosis. Changes in flow reserve after angioplasty have been inconsistent, with some patients demonstrating an immediate return to normal hyperemic/baseline flow reserve ratio and others showing little improvement or even a decrease in flow reserve ratio (3–6). Additional data obtained by using coronary artery Doppler catheters to assess stenosis severity have included measurement of ratios of post-stenotic jet velocity/normal coronary artery velocity (7). These ratios may be used to quantify the percent area stenosis by means of the continuity equation. Correlation in an animal model of stenosis was high. However, no similar human data have been reported.

Studies of phasic coronary artery flow patterns in animals (8–10) have revealed changes in the normal diastolic predominant pattern to a less diastolic predominant pattern with

From the participating institutions of the Flowmap Study: Division of Cardiology, George Washington University, Washington, D.C.; *Division of Cardiology, Saint Louis University, Saint Louis, Missouri; †Gruentzig Cardiovascular Center, Emory University, Atlanta, Georgia; ‡Sequoia District Hospital, Redwood City, California, and §Arizona Heart Institute, Phoenix, Arizona. This study was supported in part by a research grant from Cardiometrics, Inc., Mountain View, California.

Manuscript received October 16, 1991; revised manuscript received January 15, 1992, accepted February 11, 1992.

Address for correspondence: Jerome Segal, MD, Director, Cardiac Catheterization Laboratory, George Washington University Medical Center, 2150 Pennsylvania Avenue, N.W., Room 4-414, Washington, D.C. 20037.

0735-1097/92/$5.00

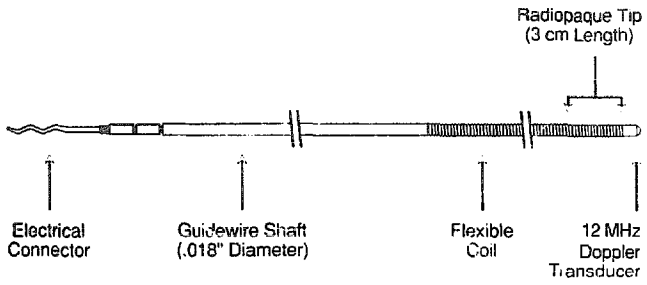


Figure 1. Diagram of Doppler coronary artery guide wire.

a greater systolic flow contribution, occurring with increasing severity of epicardial coronary artery stenosis. Recently, similar observations (11,12) were obtained in humans through the use of an 80-channel pulsed Doppler velocimeter and a surgically placed epicardial coronary artery probe. Measurements of post-stenotic velocity revealed high systolic flow components and reduced diastolic flow components. After bypass grafting, the velocity patterns distal to the graft insertion returned to a normal diastolic predominant flow pattern, with relatively little flow during systole. Such changes in diastolic and systolic flow patterns may provide important information concerning the physiologic significance of coronary artery stenosis. Unfortunately, it has been possible to obtain information concerning flow patterns distal to the site of a coronary stenosis only during open heart surgery.

We evaluated a newly developed Doppler ultrasound guide wire system capable of measuring phasic spectral flow velocity in both proximal and distal human coronary arteries during cardiac catheterization and coronary angioplasty. Measurements of flow velocity, coronary flow reserve and phasic velocity patterns obtained both proximal and distal to a coronary artery stenosis were evaluated before and after balloon angioplasty. We hypothesize that reduction in the coronary stenosis after balloon angioplasty should improve distal coronary artery flow velocity, normalize diastolic/systolic flow patterns and improve flow velocity indexes such as the diastolic/systolic velocity ratio in a manner similar to that observed after coronary artery bypass grafting.

Methods

Doppler Guide Wire

All flow velocity measurements were performed with a newly designed Doppler coronary artery flow guide wire (Cardiometrics, Inc.). This guide wire (Fig. 1) is constructed of a 175-cm long, 0.018-in. (0.046-cm) flexible, steerable, "floppy" guide wire with a 0.016-in. (0.041-cm), 12-MHz piezoelectric transducer mounted on its tip. The transducer produces a relatively broad beam (20° divergence angle) ultrasound signal, with an estimated sample volume size of 2.25 mm (diameter) at a range gate depth of 5 mm. This same guide wire has a shapable tip and was used in this study to cross a coronary stenosis and guide a standard angioplasty balloon through the coronary stenosis for dilation.

Doppler Velocimeter

The 12-MHz pulsed Doppler ultrasound velocimeter (FLOWMAP, Cardiometrics, Inc.) consisted of a real time spectral analysis system with scrolling gray-scale display. Pulse repetition frequency was variable with the velocity range selected (17 to 96 kHz), with a burst length of 0.83 μs. The Doppler system also has the capability of computing a variety of online spectral variables, including instantaneous spectral peak velocity and time-averaged spectral peak velocity. All data including the electrocardiogram (ECG) and instantaneous coronary artery pressure waveforms were recorded by using a video recorder (for video and quadrature audio outputs from the Doppler velocimeter) and a video page printer.

In vitro and in vivo validation studies. The Doppler guide wire system had been previously validated (13) both in an in vitro blood perfusion model and in in vivo animal experiments. The in vitro model utilized the Doppler guide wire to measure blood flow in five rigid tubes of known diameter (0.79, 1.59, 3.17, 4.76 and 7.94 mm, respectively). The time average of the spectral peak velocity was used for all calculations. In all five tubes, average peak velocity was highly correlated with electromagnetic flow (r^2 = 0.98 to 0.99). A quantitative estimate of flow was also calculated from Doppler velocity data using the following relation:

$$QD = \frac{(\pi D^2)}{4} AMV, \quad [1]$$

where QD = Doppler flow, D = measured tubing diameter and AMV = time-averaged mean blood flow velocity. The time-averaged mean blood flow velocity was estimated from the time-averaged spectral peak velocity (APV) using:

$$AMV = \frac{1}{2} APV \quad [2]$$

assuming a parabolic velocity profile and insonification of the internal area of the tube containing the true spatial peak velocity. Doppler guide wire-determined flow was highly correlated with electromagnetic flow over the range of 0 to 200 ml/min (Fig. 2) for all five tube sizes tested (r^2 range 0.98 to 0.99). Slopes of Doppler versus electromagnetic flow approached 1 (range 0.99 to 1.04) and intercepts were noted to be insignificant (range 0.43 to 5.0 ml/min).

In the animal experiments, Doppler flow measured in the proximal left circumflex coronary artery in four dogs was compared with electromagnetic flow. Vessel diameter was obtained by using quantitative angiography. Correlation between Doppler and electromagnetic flow remained high (r^2 = 0.94, slope = 0.85, intercept = 1.7 ml/min) for all dogs evaluated (Fig. 3).

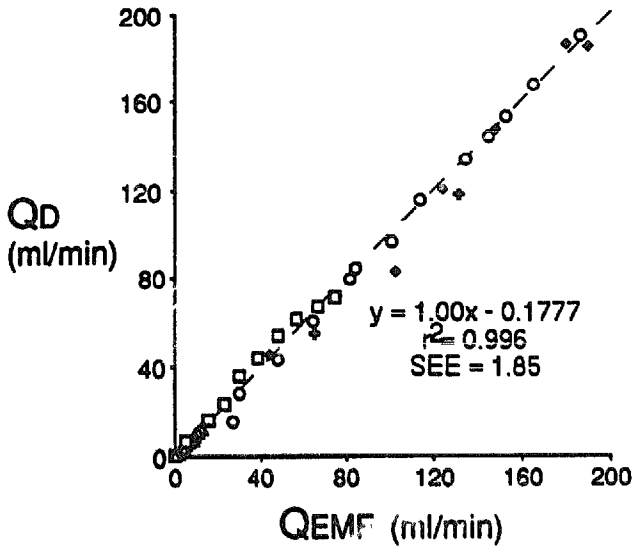
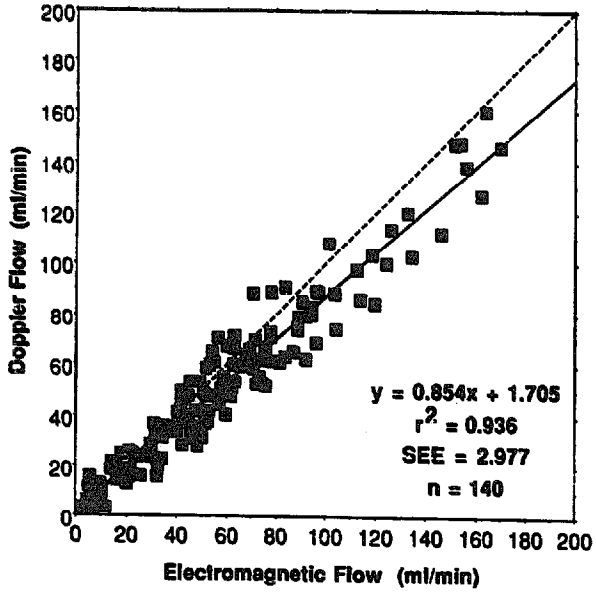


Figure 2. Plot of Doppler-determined flow versus electromagnetic flow for the in vitro flow model. △ = 0.79-mm tube; □ = 1.59-mm tube; ○ = 3.17-mm tube; ◆ = 4.76-mm tube; + = 7.94-mm tube. Reprinted from Doucette et al. (13) by permission of the American Heart Association, Inc.

Human Studies

Patient selection. Fifty patients scheduled to undergo diagnostic coronary angiography or balloon angioplasty, or both, of either the left anterior descending or the left circumflex coronary artery system were selected for the study. Patients with previous coronary artery bypass graft surgery, >50% stenosis of the left main coronary artery, acute unstable angina, acute myocardial infarction, valvular heart disease, left ventricular hypertrophy or ejection fraction <35% were excluded. The study was approved by the Human Research Committee at each of the participating institutions. All study subjects gave written informed consent. All 50 patients underwent coronary angiography. Twelve of the 50 patients had normal findings on coronary angiography and did not undergo angioplasty. Beta-adrenergic blocking drugs and calcium antagonists were not withheld. Intravenous nitroglycerin and long-acting nitrates were discontinued. Before angioplasty, all patients received 325 mg of aspirin 10,000 U of intravenous heparin, diphenhydramine (50 mg) and diazepam (5 mg) as routine premedications for angioplasty. No sublingual or intracoronary medications were given before initiating the start of the study.

Figure 3. Plot of Doppler-determined flow versus electromagnetic flow in the proximal left circumflex coronary artery in four dogs. Reprinted from Doucette et al. (13) by permission of the American Heart Association, Inc.



Coronary artery velocity measurements. All coronary artery flow velocity studies were performed by interventional cardiologists well experienced in the use of the Doppler guide wire. Once routine quantitative coronary angiography was completed, an 8F angioplasty guiding catheter was positioned in the ostium of the left main coronary artery. A continuous ECG and coronary artery pressure waveforms were recorded. The 0.018-in. Doppler guide wire was advanced through the guiding catheter and into the proximal portion of 17 angiographically normal left anterior descending or left circumflex coronary arteries in the 12 patients with no significant coronary artery disease. The Doppler guide wire was carefully positioned and torqued to obtain the maximal amplitude Doppler signal using the gray scale amplitude display. In addition to signal strength, peak instantaneous velocity was used to indicate proper positioning of the guide wire tip within the vessel. The position of the Doppler guide wire was recorded by cineangiography and phasic Doppler velocity signals were recorded before and after 9 to 12 mg of intracoronary papaverine (14) or 4 mg of intravenous adenosine (15). Velocity and pressure data were continuously recorded throughout the maximal hyperemic response and for 90 s thereafter.

In the 38 patients undergoing coronary angioplasty, the Doppler guide wire was advanced into the diseased coronary artery and positioned proximal to the stenosis beyond any large branches. Phasic velocity signals were recorded and coronary vasodilator reserve measurements were again obtained. The Doppler guide wire was advanced through the coronary stenosis and into the distal vessel while continuous phasic velocity signals were recorded. Vasodilator reserve measurements were again obtained and the position of the Doppler guide wire was documented by cineangiography.

Angioplasty protocol. The coronary artery stenosis was crossed by using an appropriately sized (2- to 3.5-mm) angioplasty balloon advanced over the Doppler guide wire. Two to five balloon inflations (6 to 10 atm for 45 to 120 s) were performed with continuous monitoring of distal flow

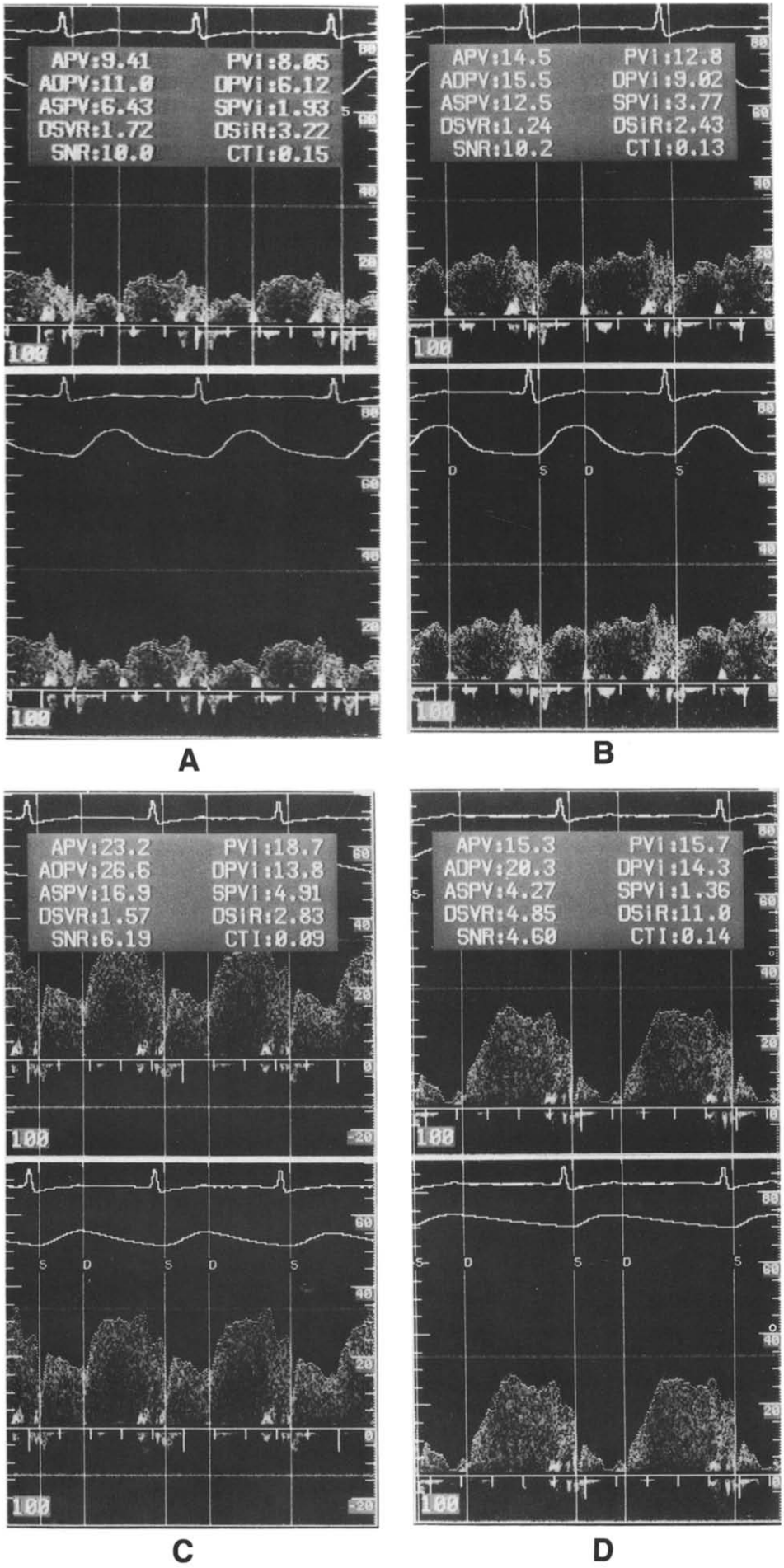


Figure 4. A, Doppler velocity measurements in the left anterior descending coronary artery proximal to a 90% stenosis. Dotted line represents instantaneous peak velocity tracking. B, Doppler velocity measurements in the left anterior descending coronary artery distal to a 90% stenosis before angioplasty. C, Doppler velocity measurements in the distal left anterior descending coronary artery 2 min after angioplasty. D, Doppler velocity measurements in the distal left anterior descending coronary artery 12 min after angioplasty. ADPV = average diastolic peak velocity; APV = time-averaged peak velocity; ASPV = average systolic peak velocity; CTI = peak tracking index; D = onset diastole; DPVi = diastolic peak velocity integral; DSiR = diastolic/systolic velocity integral ratio; DSVR = diastolic/systolic velocity ratio; PVi = peak velocity integral; SNR = signal to noise ratio; SPVi = systolic peak velocity integral; S = onset systole.

velocity during balloon inflations. Dilations were concluded when the angiographic appearance of the stenosis demonstrated >50% reduction in diameter stenosis and the residual stenosis was graded as ≤30%.

The angioplasty catheter was withdrawn under fluoroscopic guidance while the Doppler guide wire was maintained in a constant position in the distal coronary artery. Measurements of phasic velocity at baseline and during hyperemic response were obtained in the distal coronary artery 5 to 15 min after balloon deflation. The Doppler guide wire was carefully withdrawn through the residual stenosis while velocity measurements were obtained to evaluate for the presence of accelerated post-stenotic jet velocity. The Doppler guide wire was then withdrawn proximal to the dilated coronary artery segment, its position documented by cineangiography and phasic velocity and vasodilator reserve measurements repeated.

Angiographic measurements. Digital coronary artery images (Philips Medical Systems, Inc.) were manually traced. By using the guide catheter diameter as a reference, a previously described software program (16) was used to calculate vessel diameter, vessel area and percent diameter stenosis. Distal coronary artery diameter at the location of the Doppler range gate (5 mm distal to the guide wire tip) was also measured before and after angioplasty.

Peak velocity signal analysis. All relevant coronary velocity signals were recorded on videotape, along with quadrature Doppler audio signals and simultaneous ECG and coronary artery pressure waveforms. Doppler velocity spectra were analyzed on line to determine spectral peak velocity integral, time-averaged spectral peak velocity, time-averaged diastolic and systolic peak velocity (ADPV and ASPV), diastolic peak velocity integral (DPVi = area under the peak velocity curve from the aortic dicrotic notch to the systolic aortic upstroke) and systolic peak velocity integral (SPVi = area under the peak velocity curve from the systolic aortic upstroke to the aortic dicrotic notch) (Fig. 4). Diastolic/systolic flow velocity ratio was also calculated on line from time-averaged peak velocities as (ADPV/ASPV). Diastolic/systolic velocity integral ratios were calculated as (DPVi/SPVi). All velocity spectra were also analyzed offline by using a customized computer program and computer bit pad with manual tracing of video prints.

Coronary flow reserve ratio. Coronary flow reserve ratio was calculated as the maximal hyperemic average peak velocity/basal average peak velocity. Diastolic coronary flow reserve ratio was calculated as the maximal hyperemic/basal average diastolic peak velocity. Flow reserve ratio was obtained both proximal and distal to the coronary stenosis, before and after angioplasty.

Statistical analysis. *For in vitro and in vivo validation studies*, analysis of data was performed by standard linear regression, with calculation of r^2, slope, intercept and SEE.

For clinical studies, angiographic variables and velocity measurements including diastolic/systolic velocity ratio diastolic/systolic velocity integral ratio and coronary flow reserve ratio were compared by using differences between mean values and a paired one-tailed Student *t* test. Statistical significance was defined as $p < 0.05$. All data are expressed as mean value ± SD.

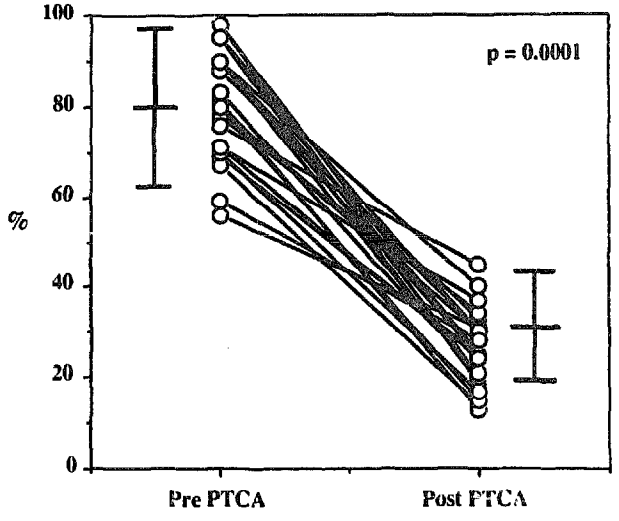


Figure 5. Percent diameter stenosis in 38 patients undergoing angioplasty (PTCA) of the left anterior descending or left circumflex coronary artery. **Horizontal bars** = mean (**widest bar**) percent stenosis ± SD. Post = after; Pre = before.

Results

Human Studies

Coronary angiographic and hemodynamic measurements. Thirty-eight coronary artery stenoses were successfully crossed with the Doppler coronary flow guide wire. Angioplasty significantly decreased the mean percent diameter stenosis from 80 ± 17% to 33 ± 23% ($p < 0.01$) (Fig. 5). Mean heart rate (76 ± 18 beats/min) and mean arterial blood pressure (95 ± 15 mm Hg) did not change significantly after angioplasty ($p > 0.10$).

Intracoronary peak velocity measurements. Stable velocity signals were obtained in the proximal and distal coronary arteries in all 50 patients (12 normal subjects and 38 patients after angioplasty). Representative phasic flow velocity spectra and simultaneous aortic pressure tracings and the ECG are illustrated in Figure 4. Average peak velocity measured in the distal coronary artery increased in most patients after angioplasty, with the mean average peak velocity increasing from 19 ± 12 to 35 ± 16 cm/s; $p < 0.01$) (Fig. 6). Because mean distal coronary artery diameter at the Doppler range gate location did not change significantly ($p > 0.10$) by quantitative angiography, improvement in distal average peak velocity was considered to be caused by an increase in distal coronary flow. A smaller percent increase in average peak velocity measured in proximal coronary arteries was also noted after angioplasty

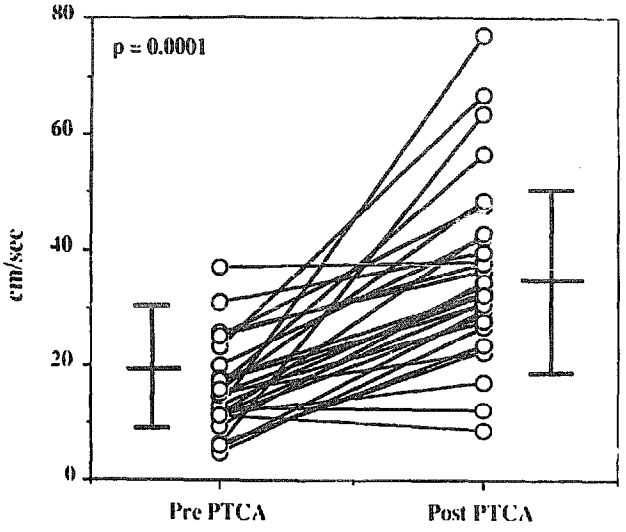
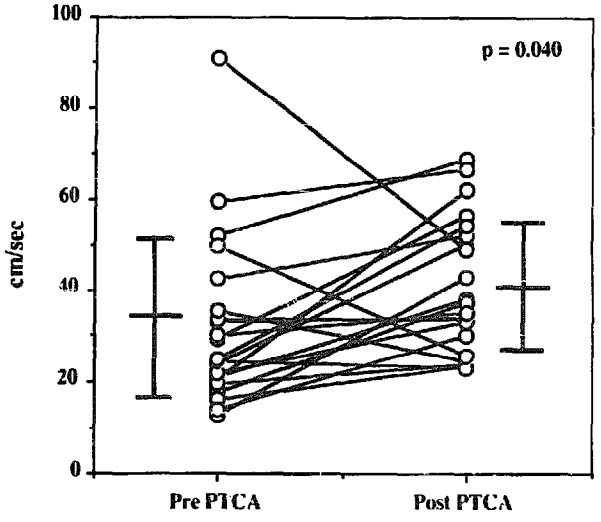


Figure 6. Time-averaged peak velocity measured distal to a coronary stenosis before and after angioplasty. **Horizontal bars** = mean **(widest bar)** of time-averaged peak velocity ± SD. Abbreviations as in Figure 5.

(from a mean value of 34 ± 16 cm/s to 41 ± 14 cm/s; p = 0.04) (Fig. 7).

Diastolic/systolic velocity patterns and ratios. Coronary arteries with significant (>70%) diameter stenosis demonstrated distal phasic velocity patterns remarkable for prominent systolic components compared with predominant diastolic components in the patterns of subjects with normal coronary arteries (Fig. 4B). Mean diastolic/systolic flow velocity ratio measured in 17 normal vessels was noted to be 1.8 ± 0.5 compared with 1.3 ± 0.5 in vessels with significant stenosis. These differences were statistically significant ($p < 0.01$), although considerable overlap was noted between the

Figure 7. Time-averaged peak velocity (± SD) measured in the proximal coronary artery, pre- and post-angioplasty. **Horizontal bars** = mean **(widest bar)** of time-averaged peak velocity ± SD. Abbreviations as in Figure 5.



patterns of normal and diseased vessels (Fig. 8B). Mean diastolic/systolic velocity integral ratio for normal and distal stenotic coronary arteries was 2.8 ± 1.1 and 2.1 ± 1.3, respectively. These ratios were statistically different (p = 0.05) (Fig. 8D).

Diastolic/systolic velocity patterns measured proximal to a significant coronary stenosis often failed to demonstrate similar abnormalities (Fig. 4A). Mean diastolic/systolic flow velocity ratio and diastolic/systolic velocity integral ratio measured proximal to a coronary stenosis were 1.8 ± 0.8 and 3.0 ± 1.6, respectively, and were not statistically different from those of normal vessels (p = 0.33 and p = 0.30, respectively) (Fig. 9, B and D).

After angioplasty, abnormal velocity patterns measured distal to the coronary stenosis generally returned to normal diastolic predominance. Mean distal diastolic/systolic flow velocity ratio after angioplasty was 1.9 ± 0.6, representing a significant ($p < 0.01$) 46% increase from values before angioplasty (Fig. 8, A and B). Similarly, mean distal diastolic/systolic velocity integral ratio after angioplasty increased to 3.1 ± 1.3, representing a 48% increase over mean values before angioplasty ($p < 0.01$) (Fig. 8, C and D). Normalization of diastolic/systolic flow patterns resulting in maximization of diastolic/systolic flow velocity ratio and diastolic/systolic velocity integral ratio required up to 10 min after angioplasty in most patients (Fig. 4, C and D).

Diastolic/systolic velocity patterns measured proximal to the coronary stenosis did not change significantly after angioplasty (Fig. 9, A and C) and mean diastolic/systolic flow velocity ratio and diastolic/systolic velocity integral ratio were not statistically different before and after angioplasty (p = 0.19 and p = 0.12, respectively) (Fig. 9, A to D).

Coronary flow reserve ratio (Table 1). In normal vessels, mean flow reserve ratio was calculated by using time-averaged peak velocity and time-averaged diastolic peak velocity; these values were 2.3 ± 0.8 for both variables. Before angioplasty the respective mean flow reserve values in stenotic coronary arteries were 1.5 ± 0.5 and 1.4 ± 0.7 measured proximally and 1.6 ± 1 and 1.5 ± 1 measured distally. Changes in flow reserve after angioplasty differed among patients; some patients demonstrated an increase and others showed no change or a decrease. No statistically significant changes were noted in mean flow reserve values after angioplasty ($p > 0.10$).

Discussion

Previous investigations (1–6,14,15,17–20) of subselective coronary artery flow measured during cardiac catheterization or angioplasty have been hindered by various methodologic problems associated with Doppler catheters. Velocity measurements in these studies were limited to large proximal segments of the coronary arteries, where flow may not be reflective of flow in more distal branches or beyond a

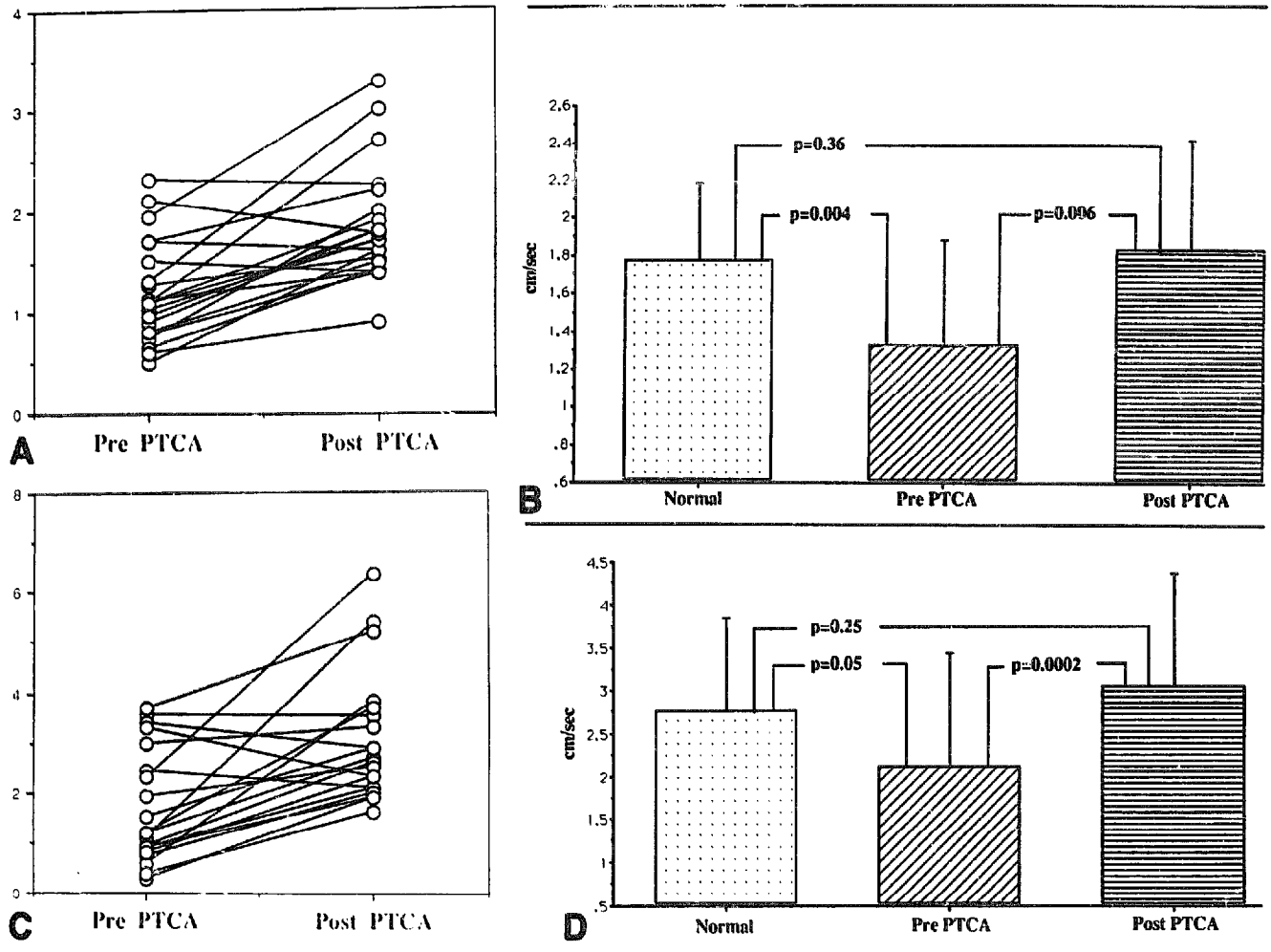


Figure 8. **A,** Diastolic/systolic velocity ratio before (Pre) and after (Post) angioplasty (PTCA) in distal coronary arteries. **B,** Mean distal diastolic/systolic velocity ratio for normal subjects and patients before and after angioplasty. **C,** Diastolic/systolic velocity integral ratio before and after angioplasty. **D,** Mean distal diastolic/systolic velocity integral ratio for normal subjects and patients before and after angioplasty.

stenosis. Animal experiments (21,22) have revealed reverse systolic flow in very distal epicardial arteries with continued forward flow in the proximal branches. Flow velocity measurements made in proximal coronary arteries beyond "major" branches and proximal to a stenosis may be influenced by flow in numerous small branches that are not considered angiographically significant. In addition, the size of the Doppler catheter relative to the size of the coronary artery and stenosis has previously been shown to create significant disturbance of flow, extending well beyond the location of the Doppler sample volume (23) and resulting in underestimation of true flow velocity.

With the use of a newly developed low profile Doppler flow guide wire with spectrally analyzed flow velocity measurements, precise changes in phasic flow velocity, systolic/diastolic velocity ratio and coronary flow reserve in distal coronary arteries were measured during angioplasty.

Changes in velocity measurements after angioplasty. Time-averaged peak velocity was shown to increase significantly (mean change 84%) in the distal coronary artery after successful coronary angioplasty. This increase was probably due to an increase in distal flow rather than to a decrease in distal coronary artery diameter because no significant change in distal coronary artery diameter at the Doppler range gate was documented by quantitative angiography after angioplasty. These increases in basal flow after angioplasty may explain the absence of significant changes in the flow ratio after angioplasty because basal and maximal hyperemic flow both increased.

Smaller percent changes in proximal average peak velocity after angioplasty were noted (mean change 20%). As previously reported (21,22), flow in proximal coronary arteries may not be reflective of flow in distal vessels. Extramural coronary arteries may act as capacitance vessels, with forward systolic flow documented in proximal segments and reverse systolic flow in distal branches. This concept of epicardial coronary capacitance and intramyocardial "pumping" has formed the basis for new models of the

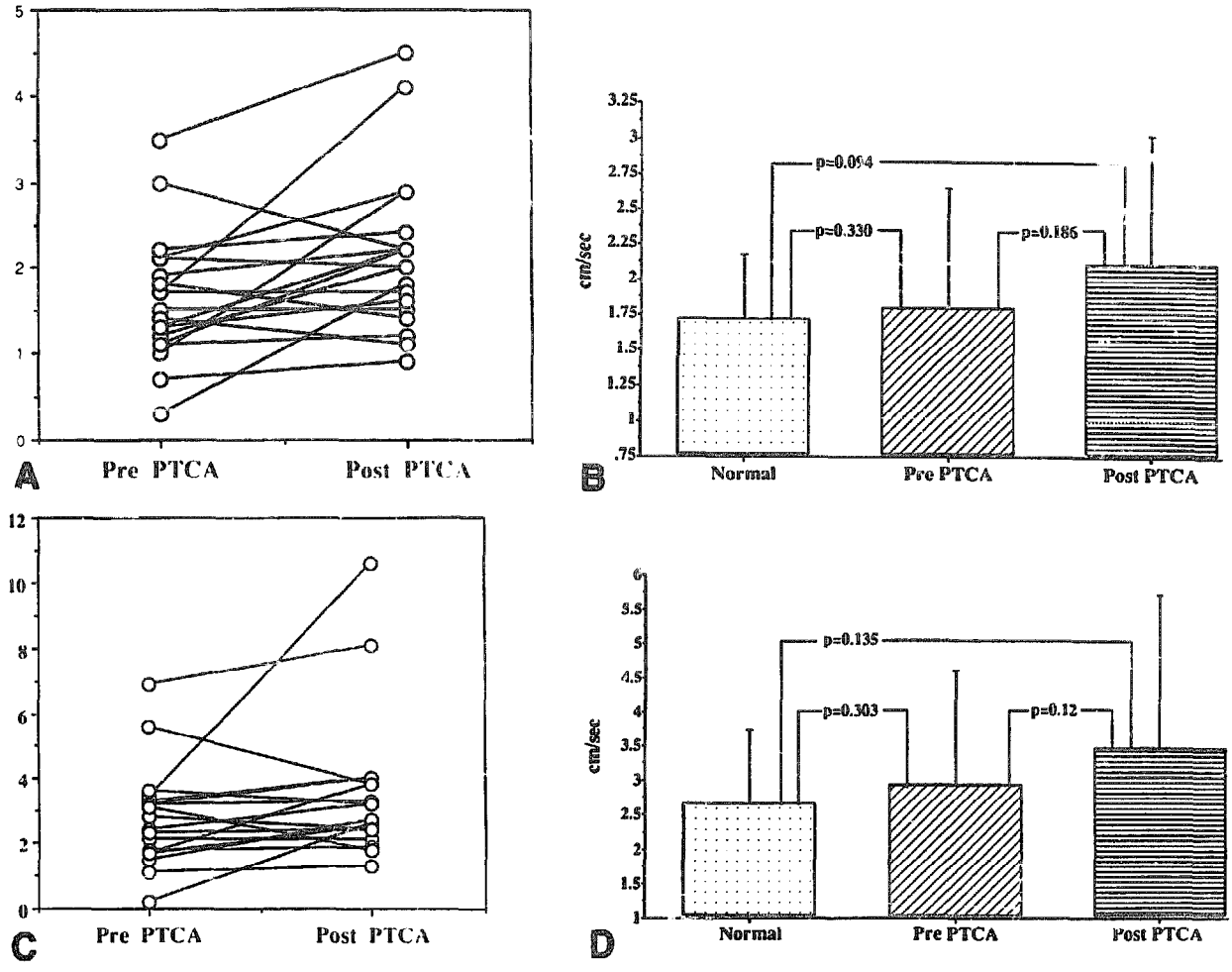


Figure 9. A, Diastolic/systolic velocity ratio before (Pre) and after (Post) angioplasty (PTCA) in the proximal coronary arteries. B, Mean proximal diastolic/systolic velocity ratio for normal subjects and patients before and after angioplasty. C, Diastolic/systolic velocity integral ratio before and after angioplasty. D, Mean proximal diastolic/systolic velocity integral ratios for normal subjects and patients before and after angioplasty.

coronary circulation (24,25). With the use of such models, significant discrepancies between instantaneous proximal coronary artery inflow and distal coronary artery outflow may be anticipated. In the current study, differences documented in average peak velocity measurements, diastolic/systolic flow patterns and diastolic/systolic velocity ratio obtained in proximal and distal coronary arteries illustrate the importance of performing such velocity measurements distal to the site of a significant coronary artery stenosis.

Coronary flow reserve and angioplasty. Previous investigations (3–6,19,26) using Doppler coronary artery catheters to perform subselective flow reserve measurements after angioplasty have obtained inconsistent results. Wilson et al. (4) reported that although papaverine-induced flow reserve increased acutely from a mean of 2.0 ± 0.1 before angioplasty to 3.6 ± 0.3 after successful angioplasty, the range of flow reserve values after angioplasty was diverse (2.5 to 7.5). Previous studies from the same laboratory (17) also documented a good correlation between angiographic degree of stenosis and coronary flow reserve in undilated coronary arteries. However, no correlation between coronary flow reserve and either angiographic percent area stenosis or minimal arterial cross-sectional area was noted after angioplasty. Kern et al. (5) reported that angioplasty did not

Table 1. Coronary Flow Reserve Ratios*

	Preangioplasty	Postangioplasty
Normal subjects (n = 17)		
APV	2.3 ± 0.8	
ADP	2.3 ± 0.8	
Stenosed vessels proximal (n = 22)		
APV	1.5 ± 0.5	1.5 ± 0.4
ADP	1.4 ± 0.7	1.5 ± 0.5
Stenosed vessels distal (n = 23)		
APV	1.6 ± 1.0	1.2 ± 0.4
ADP	1.5 ± 1.0	1.3 ± 0.6

*Measured before and after angioplasty in normal vessels, proximally in stenosed vessels and distally in stenosed vessels. Flow reserve was calculated using the ratio of hyperemic/baseline velocity measured for two different velocity ratios. All values are mean ± SD; $p > 0.05$ for all pre- versus postangioplasty measurements. ADP = time-averaged diastolic peak velocity; APV = time-averaged peak velocity.

significantly increase basal coronary artery flow velocity but did result in significantly increased papaverine-induced hyperemic response. However, papaverine-induced flow reserve calculated using any of several flow velocity indexes remained only minimally improved after angioplasty and significantly lower than that in normal vessel segments. Measurement of coronary flow reserve several weeks to months after angioplasty has yielded a more consistent relation between flow reserve and residual angiographic stenosis, with a peak/rest flow reserve ratio >3.5 in vessels with <70% stenosis (4). However, such data concerning late improvement in flow reserve are of no utility, in decision-making during the angioplasty procedure.

Our data concerning pharmacologically induced hyperemic flow reserve measured in the proximal and distal coronary arteries after angioplasty were similar to those in earlier reports. These reports also demonstrated inconsistent results, with some patients showing improvement and others showing little change. Explanations of this dissociation between coronary flow reserve and angiographic improvement after angioplasty include inaccuracies in angiographic assessment of stenosis severity, effects of collateral circulation to the affected vessel, drugs that may limit vasodilator response, abnormalities of autoregulation resulting from long-standing ischemia, release of local factors that affect coronary vasomotor tone (27,28), alteration of smooth muscle vasomotor tone due to mechanical trauma (29) and a parallel increase in baseline and hyperemic flow that would obscure any change in flow ratio. In fact, our study documented such an increase in baseline flow in the distal coronary bed after angioplasty.

Phasic flow velocity patterns and diastolic/systolic velocity ratio after angioplasty. Previous investigators (8,9) documented a reduction in the diastolic/systolic coronary flow ratio as the result of introducing an artificial coronary artery stenosis in an animal model. Similarly, studies (11,12) of diseased human left anterior descending coronary arteries during coronary bypass surgery using an 80-channel pulsed Doppler probe revealed a marked reduction in diastolic flow velocity and unchanged systolic flow velocity during graft occlusion. This decrease in diastolic/systolic velocity ratio with increasing degree of epicardial stenosis may be explained by the increased influence of an epicardial stenosis on flow during periods of low distal vascular resistance (diastole) as compared with that during periods of high distal vascular resistance (systole) (30). Alternative explanations using the intramyocardial "pump" model of Spaan et al. (24) suggest that epicardial resistance will become the limiting factor for anterograde coronary flow during periods of no reverse intramyocardial flow and low distal arterial and venous resistance (diastole). However, during systole, reverse coronary flow from the intramyocardial pump continues to "charge" the epicardial coronary capacitance at the expense of increasing the transstenotic (aortic-intramyocardial) pressure difference. The influence of increasing forward flow resistance (due to the epicardial stenosis) and increasing reduction in transstenotic pressure tend to cancel each other, resulting in little flow change during systole.

Phasic coronary artery flow waveforms in the distal coronary artery beyond a significant stenosis were easily characterized with the Doppler flow guide wire. The data in a closed chest human model confirm the intraoperative findings of Kajiya et al. (11,12). With significant (>70%) diameter stenosis, diastolic flow components appeared significantly reduced, whereas systolic flow components were less affected. After relief of the stenosis after angioplasty, diastolic flow and diastolic/systolic velocity ratio increased significantly whereas systolic flow increased less. In several cases, diastolic/systolic velocity ratio required up to 10 min to reach the maximal value (Fig. 4). This time delay may be explained by impaired immediate normalization of autoregulation in diseased precapillary arteries (31,32), inhibition or release of local or endothelial vasomotor factors (33,34) or delayed recovery of systolic contraction of the regional myocardium with slow recovery of intramyocardial pump function after the relief of chronic ischemia. Normalization of diastolic/systolic flow velocity ratio after angioplasty paralleled angiographic improvement, implying improved subendocardial perfusion after successful angioplasty. Further studies will be required to determine whether such improvement in this ratio is predictive of improvement in regional myocardial function or clinical outcome after successful angioplasty.

Limitations

Doppler guide wire positioning. The Doppler flow guide wire provides a convenient means of obtaining phasic flow velocity data in both proximal and distal coronary arteries. However, it has several specific limitations. Placement of the guide wire for optimization of signal strength is necessary. As noted in the Methods section, the Doppler guide wire was manipulated by using the gray scale signal amplitude and peak velocity as indicators of proper positioning within the vessel. In tortuous coronary segments or if the guide wire tip is preformed into a significant curve, significant manipulation may be required to point the transducer away from the vessel wall and into the flow stream. Occasionally, vessel wall artifact cannot be avoided and the guide wire must be repositioned into an alternative segment of the vessel.

In large vessels in which the guide wire is angled, the ultrasound beam may not intercept the true maximal flow velocity. Repositioning or manipulation of the guide wire will result in some variation in measured peak velocity in these cases and errors in reproducibility of Doppler velocity measurements will occur.

Flow velocity profiles. In normal proximal coronary arteries, the flow velocity profile is generally parabolic (11,12). However, significant flow separation with turbulence has been demonstrated (11,12,35) in the coronary region immediately beyond a significant stenosis. In the more distal

coronary artery (>5 diameter lengths) beyond a stenosis, relaminarization of flow is expected to occur. It is at this location that our "distal" flow measurements were obtained. However, changes in the distal velocity profile may be anticipated after relief of a significant stenosis with balloon angioplasty. These changes in the distal velocity profile would introduce inconsistency in the comparison of any velocity measurements performed before and after angioplasty. Although the degree of such inconsistency would be expected to be small, its exact magnitude is not known.

Coronary flow reserve measurements. Measurements of mean coronary flow reserve in normal patients in the current study were lower than values previously reported by some investigators (14,17,19) utilizing Doppler catheters and comparable to those of others (5,15,36,37). Given the excellent correlation of Doppler guide wire velocity measurements to electromagnetic flow in in vivo and in vitro validation studies (13) and in human studies (38) comparing the Doppler guide wire with Doppler coronary catheters, these low flow reserve values are unlikely to be due to inaccuracies in Doppler guide wire velocity measurements. Bolus administration of adenosine in some of our patients may not have produced a maximal coronary vasodilator response compared with that after intracoronary papaverine. However, our flow reserve values were comparable to values after bolus adenosine administration in normal subjects (15) and were significantly higher than flow reserve measurements in our patients with coronary artery disease. Lower values for flow reserve in the current study may also be attributed to differences in technique of flow velocity measurement. Previously reported studies utilizing Doppler catheters and zero cross frequency detection techniques have variably defined coronary flow reserve ratio as the ratio of peak frequency shift (after drug administration) to frequency shift at rest (1,19) or as mean flow velocity (after stimulation) to mean flow velocity at rest (5,14,15). The current study defines coronary flow reserve as the ratio of the spectral peak velocities averaged over two complete cardiac cycles. Spectral analysis techniques have been shown (11,12,23) to be more accurate in estimating true peak flow velocity than zero cross techniques, specifically in disturbed flow fields (11,12,23). Additionally, spectral techniques are less subject to error introduced by "wall thump" artifact.

Coronary flow reserve measurements were obtained with the guiding catheter still engaged in the coronary ostium, which may have resulted in partial ischemia and limited flow reserve, even in normal subjects. Finally, our group of "normal subjects" may have included some patients with angiographically normal coronary arteries with microcirculatory abnormalities due to hypertension, left ventricular hypertrophy, diabetes or cardiac transplantation.

Conclusions. The Doppler flow guide wire appears capable of characterizing phasic diastolic and systolic flow velocity patterns in both proximal and distal coronary arteries and may be easily incorporated into the clinical angioplasty procedure. Discrepancies were noted between phasic flow velocity measurements made proximal to a coronary stenosis and those in the distal coronary artery. These differences highlight the importance of making velocity measurements distal to a lesion if distal myocardial perfusion is to be accurately assessed. Coronary flow reserve measurements made immediately after angioplasty were of limited utility in assessing the hemodynamic effect of the procedure, regardless of whether the hyperemic response was measured in the proximal or distal coronary artery. Alternative measurements made in the distal vessel, such as the change in absolute distal flow velocity or in diastolic/systolic velocity ratio after angioplasty, appear to be more relevant in predicting the clinical outcome of the procedure. Additional studies are required to assess these newer flow velocity variables in patients.

We thank Drs. Conor F. Lundergan, William Herzog and Ashis Mukherjee for their assistance in performing these studies. We also thank Jan St. Vrain, Andrew J. Ford, P. Douglas Corl, Menachem Nasi, Helene M. Payne and Shyuan Cho for their technical assistance, and Beth Marshall and Beth Rogers for their help in the preparation of the manuscript.

References

1. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;210:819–24.
2. Harrison DG, White C, Hiratzka LF, et al. The value of lesion cross-sectional area determined by quantitative coronary angiography in assessing the physiologic significance of proximal left anterior descending coronary arterial stenosis. Circulation 1984;69:1111–9.
3. Serruys PW, Julliere Y, Zijlstra F, et al. Coronary blood flow velocity during percutaneous transluminal coronary angioplasty as a guide for assessment of the functional result. Am J Cardiol 1988;61:253–9.
4. Wilson RF, Johnson MJ, Talman CL, et al. The effect of coronary angioplasty on coronary flow reserve. Circulation 1986;76:873–85.
5. Kern MJ, Deligonul U, Vandormael M, et al. Impaired coronary vasodilator reserve in the immediate postcoronary angioplasty period: analysis of coronary artery flow velocity indexes and regional cardiac venous efflux. J Am Coll Cardiol 1989;13:860–72.
6. Kern MJ, Presant S, Deligonul U, Vandormael M, Kennedy HL. The effects of coronary angioplasty on nitroglycerin-induced augmentation of regional myocardial flood flow. J Intervent Cardiol 1988;1:121–30.
7. Johnson EL, Yock PG, Hargrave VK, et al. Assessment of severity of coronary stenoses using a Doppler catheter: validation of a method based on the continuity equation. Circulation 1989;80:625–35.
8. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Am J Cardiol 1974;33:87–94.
9. Furuse A, Klopp EH, Brawley RK, Gott VL. Hemodynamic determinations in the assessment of distal coronary artery disease. J Surg Res 1975;19:25–33.
10. Wiesner TF, Levesque MJ, Rooz E, Nerem RM. Epicardial coronary blood flow including the presence of stenoses and aorto-coronary bypasses. II. Experimental comparison and parametric investigations. Trans ASME 1988;110:144–9.
11. Kajiya F, Ogasawara Y, Tsujioka K, et al. Evaluation of human coronary blood flow with an 80 channel 20 MHz pulsed Doppler velocimeter and zero-cross and Fourier transform methods during cardiac surgery. Circulation 1986;74(suppl III):III-53–60.
12. Kajiya F, Ogasawara Y, Tsujioka K, et al. Analysis of flow characteristics in post-stenotic regions of the human coronary artery during bypass graft surgery. Circulation 1987;76:1092–100.
13. Doucette JW, Corl PD, Payne HM, et al. Validation of a Doppler guidewire for intravascular measurement of coronary artery flow velocity. Circulation 1992;85:1899–911.

14. Wilson RF, White C. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation 1986;73:444–51.
15. Kern MJ, Deligonol V, Tatineni S, Serota H, Aguirre F, Hilton TC. Intravenous adenosine: continuous infusion and low dose bolus administration for determination of coronary vasodilator reserve in patients with and without coronary artery disease. J Am Coll Cardiol 1991;18:718–29.
16. Reiber JHC, van der Zwet PMJ, von Land CD, et al. On-line quantification of coronary arteriograms with the DCI system. Medicamundi 1989; 34:89–98.
17. Wilson RF, Laughlin DE, Ackell PH, et al. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 1985;72:82–92.
18. Sibley DH, Millar HD, Hartley CJ, Whitlow PL. Subselective measurement of coronary blood flow velocity using a steerable Doppler catheter. J Am Coll Cardiol 1986;8:1332–40.
19. Wilson RF, Marcus ML, White C. Prediction of the physiologic significance of coronary arterial lesions by quantitative lesion geometry in patients with limited coronary artery disease. Circulation 1987;75:723–32.
20. Kern MJ, Pearson AC, Labovitz AJ, Deligonul U, Vandormael M, Gudipati C. Effects of pharmacologic coronary hyperemia on echocardiographic left ventricular function in patients with single vessel coronary artery disease. J Am Coll Cardiol 1989;13:1042–51.
21. Chillan WM, Marcus ML. Effects of coronary and extravascular pressure on intramyocardial and epicardial blood velocity. Am J Physiol 1985;248: H170–8.
22. Kajiya F, Tomonaga G, Tsujioka K, Ogasawara Y, Nishhara H. Evaluation of local blood flow velocity in proximal and distal coronary arteries by laser Doppler method. J Biomech Engin 1985;107:10–5.
23. Tadaoka S, Kagiyama M, Hiramatsu O, et al. Accuracy of a 20 MHz Doppler catheter coronary velocimeter for measurement of coronary blood flow velocity. Cathet Cardiovasc Diagn 1990;12:205–13.
24. Spaan JAAE, Breuls NPW, Laird JD. Diastolic-systolic coronary flow differences are caused by intramyocardial pump action in the anesthetized dog. Circ Res 1981;49:584–93.
25. Lee J, Chambers DE, Akizuki S, Downey JM. The role of vascular capacitance in the coronary arteries. Circ Res 1984;55:751–62.
26. Wilson RF, Marcus ML, White C. Effects of coronary bypass surgery and angioplasty on coronary blood flow and flow reserve. Prog Cardiovasc Dis 1988;3:95–114.
27. Furchgott RF, Zawadzki JV. The obligator role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288: 373–6.
28. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046–51.
29. Waller BF. Early and late morphological changes in human coronary arteries after percutaneous transluminal coronary angioplasty. Clin Cardiol 1983;6:363–72.
30. Logan SE. On the fluid mechanics of human coronary artery stenosis. IEEE Trans Biomed Engin 1975;22:327–34.
31. Macho P, Hintze TH, Vatner SF. Regulation of large coronary arteries by increases in myocardial metabolic demand in the conscious dog. Circ Res 1981;49:594–9.
32. Olsson RA. Myocardial reactive hyperemia. Circulation 1975;37:263–70.
33. Holtz J, Forstermann U, Pohl U, Glesler M, Bassenge E. Flow dependent endothelial medicated dilation of epicardial arteries in the conscious dog: effects of cyclooxygenase inhibition. J Cardiovasc Pharmacol 1984;6: 1161–9.
34. Inoue T, Tomoike H, Hisanok K, Nakamura M. Endothelium determines flow-dependent dilation of the epicardial coronary artery in dog. J Am Coll Cardiol 1988;11:187–91.
35. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. Circ Res 1990;66:1045–66.
36. Hodgson JM, Riley RS, Mos. AS, Williams DO. Assessment of coronary flow reserve using digital angiography before and after successful percutaneous transluminal coronary angioplasty. Am J Cardiol 1987;60:61–5.
37. Dole WP, Richards KL, Hartley CJ, Alexander GM, Campbell AB, Bishop VS. Diastolic coronary artery pressure-flow velocity relationships in conscious man. Cardiovasc Res 1984;18:548–54.
38. Ofili E, Karim AM, Kern MJ, et al. Simultaneous comparison of intracoronary spectral and zero cross flow velocity measurements by Doppler angioplasty guidewire and catheter techniques (abstr). J Am Coll Cardiol 1991;17(suppl A):124A.